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Pharmacokinetics of percutaneous absorption with concurrent metabolism

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Summary

A pharmacokinetic model for percutaneous absorption has been formulated which allows calculation of the drug disposition in the skin, plasma and urine. Allowance is also made for metabolic processes within the skin. The influence of metabolism on the concentrations of the parent molecule and the metabolite in the plasma is discussed.

Introduction

In a previous publication (Guy et al., 1982) we have identified a pharmacokinetic model to describe the process of percutaneous absorption. In this treatment a linear model was used in which no account of drug metabolism was taken. Using the technique we (Anjo et al., 1980) were able to predict urinary excretion data for 3 topically applied drugs: hydrocortisone, testosterone and benzoic acid. The rate constants used in the pharmacokinetic analysis were related to the physicochemical properties of the 3 compounds.

However, many drugs may be subject to metabolism as they diffuse through the layers of the epidermis. Wester and Noonan (1980) state that the enzymes present in skin may have real activities in the range 80–120% of those of the liver. For this reason it was felt desirable to modify the straightforward pharmacokinetic model to take account of metabolism. In this way it is possible to predict theoretically the

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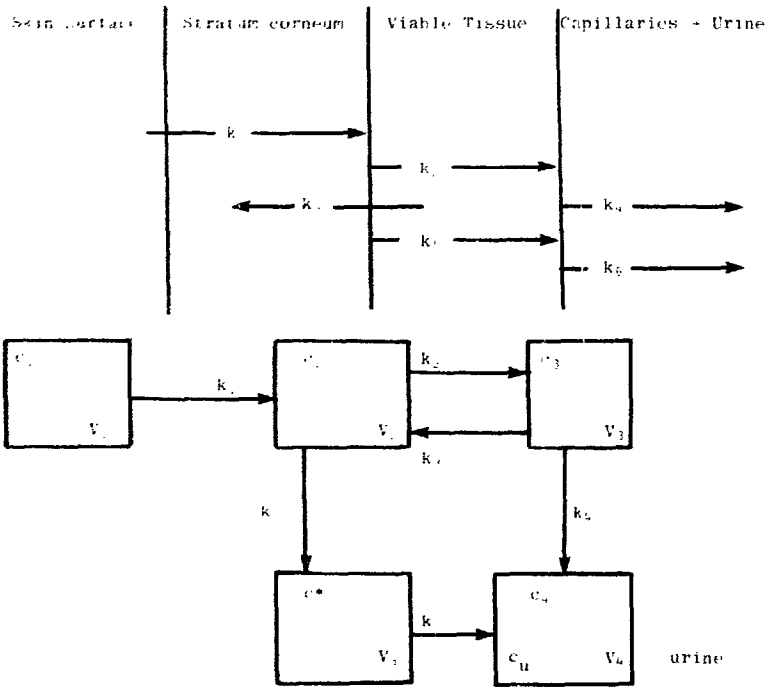
levels of the parent drug and metabolite in the plasma. Information of this type is useful in assessing drugs for both local and percutaneous systemic therapy. The recent interest in the use of topical prodrugs has also provoked an interest in the effects of percutaneous metabolism and this model will be important in assessing the effectiveness of the prodrug approach to topical therapy.

In the model we assume, as previously, that first-order rate constants are appropriate. It would be possible to solve the mathematics for more complex kinetic behaviour but it would be difficult to find data of sufficient accuracy to justify modelling rate processes other than first-order.

The model

The pharmacokinetic scheme is represented in Scheme 1. In this diagram k_1 through k_4 have the same significance as in our previous description. k_1 characterizes the absorption phase and we assume is limited by the diffusion of drug across the stratum corneum. The second rate constant, k_2, describes the deeper penetration of the drug into and through the viable epidermis. An estimate of the magnitude of k_2 can be obtained by considering diffusion of the drug through an aqueous protein gel. k_3 is more complex and reflects the competition for the drug between the primarily lipophilic nature of the stratum corneum and the hydrophilic viable epidermis. For drugs which bind strongly with components of the stratum corneum or those which have high oil/water partition coefficients k_3 will be large.



Schema 1. Schematic representation of the pharmacokinetic model.

The elimination rate constant, k_4, describes the removal of the drug into the urine once it has reached the dermal vasculature. In order to simplify solution of the equations no attempt has been made to delineate the material in the cutaneous capillaries and that in the general circulation. Thus k_4 is the same as the elimination rate constant for materials administered by an intravenous route.

We then refine the model further by including a metabolic step represented by k_5 and subsequent removal of the metabolite k_6. In order to simplify the solution of the equations k_5 has been assigned as a first-order rate constant. Thus, if the enzyme is metabolically active and follows Michaelis-Menten kinetics the representation in this model is only valid for small substrate concentrations. In reality this is probably a valid approximation.

Theory

The solution of the kinetic scheme given in Scheme 1 is relatively straightforward. Rate equations for the different compartments can be written:

$$\frac{dc_1}{dt} = -k_1c_1 \tag{1}$$

$$\frac{dc_2}{dt} = \frac{V_1}{V_2} \cdot k_1c_1 - k_2c_2 + \frac{V_3}{V_2}k_3c_3 - k_5c_2 \tag{2}$$

$$\frac{dc_3}{dt} = \frac{V_2}{V_3} \cdot k_2c_2 - k_3c_3 - k_4c_3 \tag{3}$$

$$\frac{dc_4}{dt} = \frac{V_3}{V_4} \cdot k_4c_3 \tag{4}$$

$$\frac{dc^*}{dt} = \frac{V_2}{V_3} \cdot k_5c_2 - k_6c^* \tag{5}$$

$$\frac{dc_u^*}{dt} = \frac{V_3}{V_4} \cdot k_6c^* \tag{6}$$

These simultaneous first-order kinetic equations are solved by Laplace transformation. The transformed equations are:

$$s\bar{u} - 1 = -k_1\bar{u}_1 \tag{7}$$

$$s\bar{u}_2 = \frac{V_1}{V_2}k_1\bar{u}_1 - k_2\bar{u}_2 + \frac{V_3}{V_2} \cdot k_3\bar{u}_3 - k_5\bar{u}_2 \tag{8}$$

$$s\bar{u}_3 = \frac{V_2}{V_3} \cdot k_2\bar{u}_2 - k_3\bar{u}_3 - k_4\bar{u}_3 \tag{9}$$

$$s\bar{u}_4 = \frac{V_3}{V_4} \cdot k_4\bar{u}_3 \tag{10}$$

$$s\bar{u}^* = \frac{V_2}{V_3} \cdot k_5\bar{u}_2 - k_6\bar{u}^* \tag{11}$$

$$s\bar{u}^*_u = \frac{V_3}{V_4} \cdot k_6\bar{u}^* \tag{12}$$

where we have expressed the concentration in terms of a normalized variable.

$$u_i = c_i/c_0 \qquad (i = 1, 2, 3, 4, *) \tag{13}$$

where c_0 is the concentration in compartment i at time $t = 0$. It is possible to solve Eqns. 7–12 by repeated substitution to obtain values of the concentrations in any of the compartments. For the purposes of comparison it is probably best to consider the relative amounts of parent compound and metabolite that are established in the blood supply, i.e. u_3 and u^*. Inverting the Laplace transforms gives:

$$u_3 = \frac{V_1k_1k_2}{V_3}\left(\frac{\exp(-\alpha t)}{(\beta-\alpha)(k_1-\alpha)} + \frac{\exp(-\beta t)}{(\alpha-\beta)(k_1-\beta)} + \frac{\exp(-k_1 t)}{(\alpha-k_1)(\beta-k_1)}\right) \tag{14}$$

where α and β are the roots of the quadratic equation

$$s^2 + s(k_2 + k_3 + k_4 + k_5) + k_3k_5 + k_2k_4 + k_4k_5 = 0$$

For the metabolite concentrations,

$$u^* = \frac{V_1k_1k_5}{V_3}(A_1(t) + A_2(t) + A_3(t) + k_2k_3A_4(t) + A_5(t) + A_6(t)$$

$$+ A_7(t) + A_8(t) \tag{15}$$

where

$$A_1(t) + \frac{\exp(-k_1 t)}{(\gamma-k_1)(k_6-k_1)} \tag{16}$$

$$A_2(t) = \frac{\exp(-\gamma t)}{(k_1-\gamma)(k_6-\gamma)} \tag{17}$$

$$A_3(t) = \frac{\exp(-k_6 t)}{(k_1 - k_6)(\gamma - k_6)} \quad (18)$$

$$A_4(t) = \frac{\exp(-k_1 t)}{(\alpha - k_1)(\beta - k_1)(\gamma - k_1)(k_6 - k_1)} \quad (19)$$

$$A_5(t) = \frac{\exp(-\alpha t)}{(k_1 - \alpha)(\beta - \alpha)(\gamma - \alpha)(k_6 - \alpha)} \quad (20)$$

$$A_6(t) = \frac{\exp(-\beta t)}{(k_1 - \beta)(\alpha - \beta)(\gamma - \beta)(k_6 - \beta)} \quad (21)$$

$$A_7(t) = \frac{\exp(-\gamma t)}{(k_1 - \gamma)(\alpha - \gamma)(\beta - \gamma)(k_6 - \gamma)} \quad (22)$$

$$A_8(t) = \frac{\exp(-k_6 t)}{(k_1 - k_6)(\alpha - k_6)(\beta - k_6)(\gamma - k_6)} \quad (23)$$

where $\gamma = (k_2 + k_5)$

Applications of the model

Using eqns. 14 and 15, it is possible to calculate plasma levels of the drug and metabolite for various combinations of the rate constants. The choice of the rate constants is wide but certain constraints may be imposed. In our previous publication (Guy et al., 1982) we identified values of k_1, k_2, k_3, k_4 for benzoic acid.

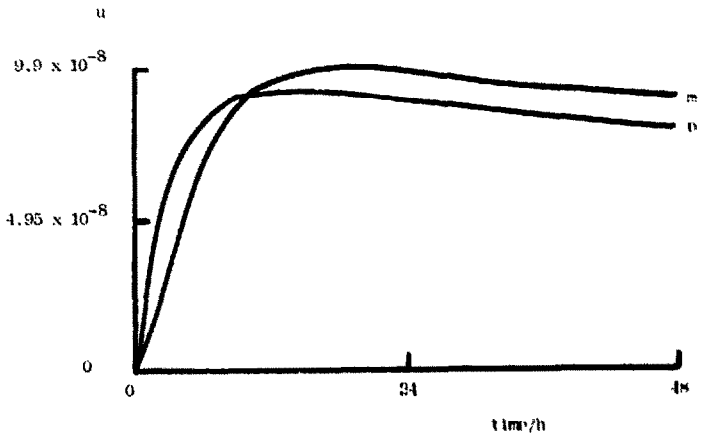


Fig. 1. The fraction of applied topical dose appearing in the plasma as parent compound (p) and metabolite (m) as a function of time for the following 1st-order rate constants (s^{-1}). $k_1 = 10^{-6}$; $k_2 = k_3 = 10^{-3}$; $k_4 = k_5 = k_6 = 10^{-4}$.

TABLE 1
THE RANGE OF VALUES FOR THE DIFFERENT RATE CONSTANTS IN THE PHARMACOKINETIC MODEL

Rate constants	Values (s^{-1})
k_1	$10^{-5} \rightarrow 10^{-6}$
k_2	$10^{-3} \rightarrow 10^{-4}$
k_3	$10^{-3} \rightarrow 10^{-6}$
k_4	$10^{-4} \rightarrow 10^{-5}$
k_5	$10^{-4} \rightarrow 10^{-6}$
k_6	$10^{-4} \rightarrow 10^{-5}$

hydrocortisone and testosterone. These values should give a sufficient span of physicochemical properties for investigating possible effects of metabolism. The rate constants k_4 and k_6 would be expected to be of a similar order of magnitude. k_5 is more difficult to ascribe but values in the range 5×10^{-5} s^{-1} would not be unreasonable (Hadgraft, 1980; Tauber and Toda, 1976). The range of values for the rate constants chosen for the analysis is given in Table 1. The ratio V_1/V_3 has been assigned a value of 2×10^{-5} based on an applied volume of 100 μl and a plasma volume of 5 litres.

Hence different combinations of the rate constants can be taken and the effects of metabolism noted. The plasma profiles for different 'typical' combinations are presented in Figs. 1–8.

It may be seen that under many circumstances the concentration of the metabolite is higher than that of the parent drug. It is also instructive to compare different figures. For example, a comparison of Figs. 2 and 5 shows the effect of altering the diffusion process through the stratum corneum. The values of k_1 in the two figures represent a 10-fold difference in the diffusion coefficient of the drug. For the smaller diffusion coefficient the peak plasma levels are lower but more sustained. Metabo-

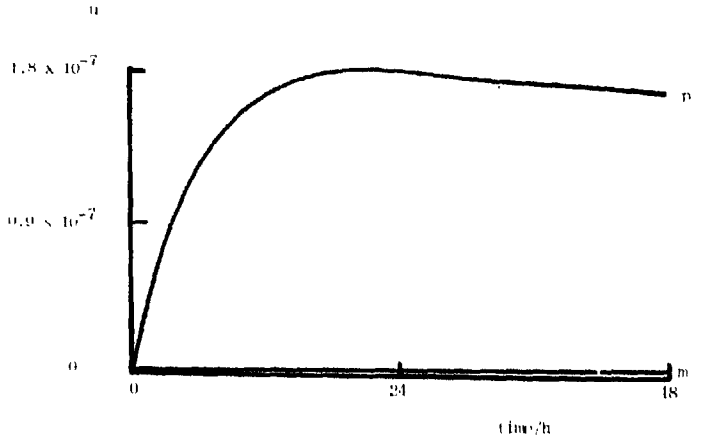


Fig. 2. The fraction of applied topical dose appearing in the plasma as parent compound (p) and metabolite (m) as a function of time for the following 1st order rate constants (s^{-1}). $k_1 = k_5 = 10^{-6}$; $k_2 = k_3 = 10^{-3}$; $k_4 = k_6 = 10^{-4}$.

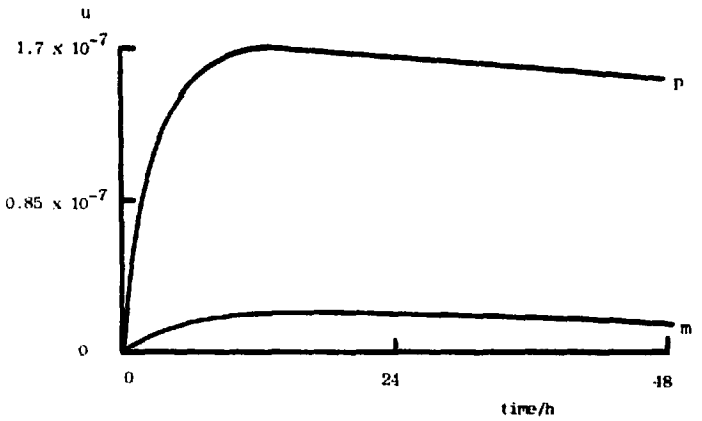


Fig. 3. The fraction of applied topical dose appearing in the plasma as parent compound (p) and metabolite (m) as a function of time for the following 1st-order rate constants (s^{-1}). $k_1 = k_3 = 10^{-6}$; $k_2 = 10^{-3}$; $k_4 = k_5 = k_6 = 10^{-4}$.

lism in both these cases is insignificant Similarly Figs. 1 and 7 compare transport through the viable epidermis. With slower transit times in this region the effect of metabolism is more pronounced and the metabolite levels are considerably higher.

Figs. 1 and 3 and Figs. 2 and 8 compare the partitioning between the stratum corneum and the viable epidermis, i.e. the ratio k_3/k_2. Where metabolism is small and diffusion in the stratum corneum is low (Figs. 2 and 8) partitioning does not affect the overall plasma levels significantly. However, in Figs. 1 and 3 where the metabolic rate is high the role of partitioning is quite important and should be considered in topical drug delivery.

A comparison of the effect of k_5, the metabolic rate is seen in Figs. 1 and 2, 3, and 8, 4 and 5. Where partitioning is low (Figs. 3 and 8), the effect of metabolism is not so marked. Overall, it is possible to see that a hundred-fold increase in the metabolic rate has a considerable effect on the ratio of metabolite/parent drug in the plasma.

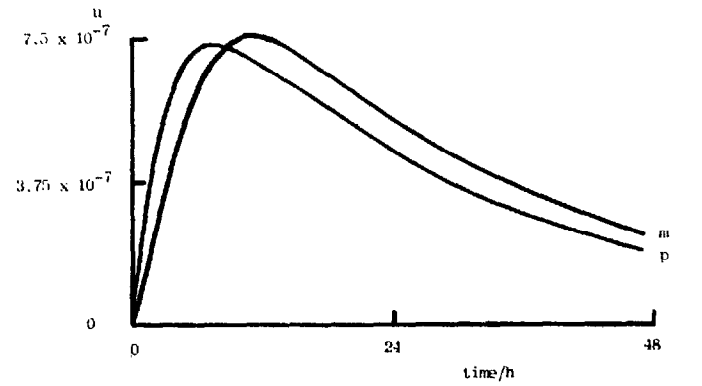


Fig. 4. The fraction of applied topical dose appearing in the plasma as parent compound (p) and metabolite (m) as a function of time for the following 1st-order rate constants (s^{-1}). $k_1 = 10^{-5}$; $k_2 = k_3 = 10^{-3}$; $k_4 = k_5 = k_6 = 10^{-4}$.

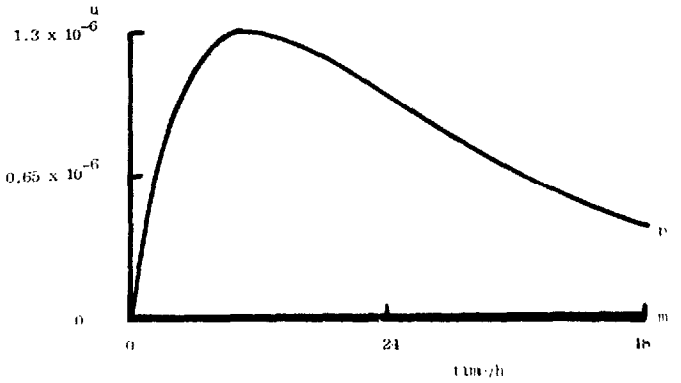


Fig. 5. The fraction of applied topical dose appearing in the plasma as parent compound (p) and metabolite (m) as a function of time for the following 1st-order rate constants (s^{-1}). $k_1 = 10^{-5}$; $k_2 = k_3 = 10^{-3}$; $k_4 = k_6 = 10^{-4}$; $k_5 = 10^{-6}$

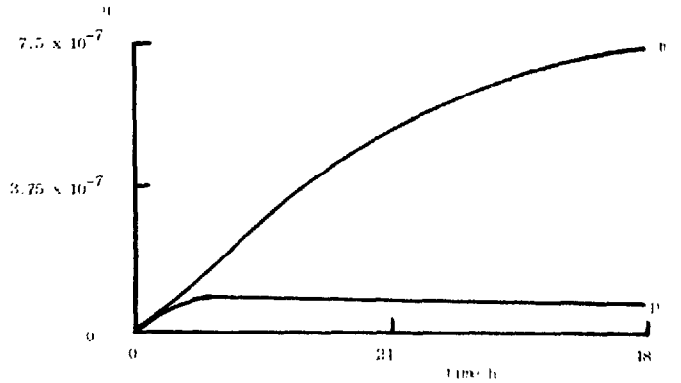


Fig. 6. The fraction of applied topical dose appearing in the plasma as parent compound (p) and metabolite (m) as a function of time for the following 1st-order rate constants (s^{-1}). $k_1 = 10^{-6}$; $k_2 = k_3 = 10^{-3}$; $k_4 = k_5 = 10^{-4}$; $k_6 = 10^{-5}$

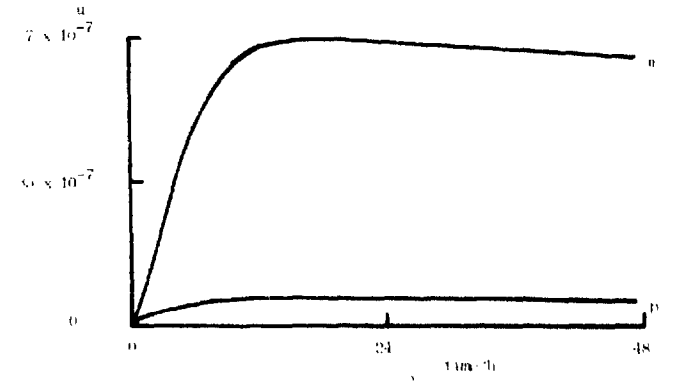


Fig. 7. The fraction of applied topical dose appearing in the plasma as parent compound (p) and metabolite (m) as a function of time for the following 1st-order rate constants (s^{-1}). $k_1 = 10^{-6}$; $k_2 = k_4 = k_5 = k_6 = 10^{-4}$; $k_3 = 10^{-3}$.

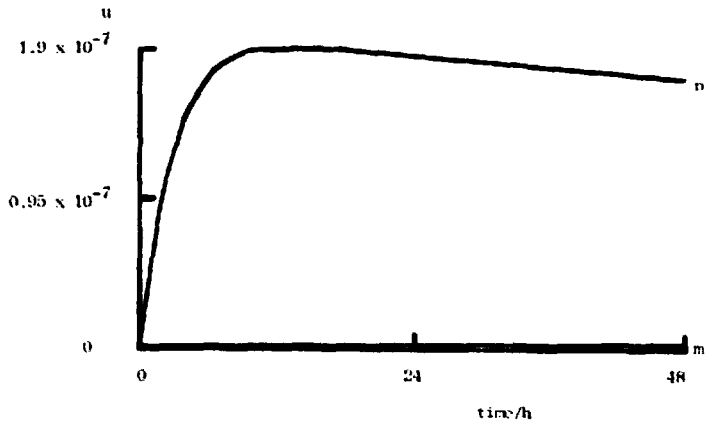


Fig. 8. The fraction of applied topical dose appearing in the plasma as parent compound (p) and metabolite (m) as a function of time for the following 1st-order rate constants (s^{-1}). $k_1 = k_3 = k_5 = 10^{-6}$; $k_2 = 10^{-3}$; $k_4 = k_6 = 10^{-4}$.

It is also possible to see the effect of slow metabolite diffusion in the viable epidermis: Figs. 1 and 6. For slow diffusion the parent/metabolite ratio is modified by a large amount. Thus care should be taken in the design of a prodrug to ensure that the correct diffusion properties are found.

This type of analysis will be useful in assessing problems created by unwanted metabolism of active drug and also in the rational design of novel prodrugs. Data is becoming available which shows the extent of metabolism of topically applied substances and using this type of approach it will be possible to analyse this data.

Acknowledgements

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